PHARMACEUTICAL PREPARATION FOR THE ORAL CAVITY

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BACKGROUND OF THE INVENTION

[0001] The invention relates generally to a pharmaceutical preparation for the oral cavity, the preparation being in the form of an aqueous solution that is buffered to a physiological pH and provided with anti-inflammatory and analgesic activity. The preparation is particularly suitable for spraying into the oral cavity by means of a suitable dosing pump.

[0002] For around a decade now, the incidence of generalised inflammatory conditions of the throat, mouth and gums has been on the increase, especially during the winter. These very troublesome conditions are not generally attributable to a specific cause, but may arise due to various external factors, such as for example, sudden changes in ambient temperature, irritant or toxic substances contained in the air or in polluted environments, and direct or indirect inhalation of cigarette smoke. Such conditions may also be attributable to internal factors, such as for example, slight infections with viruses, echoviruses, macro viruses or bacteria or, as frequently occurs, due to the simultaneous presence of one or more of these irritants. The resultant clinical picture is thus highly complex, with inflammation and pain predominating among the many symptoms. Since it is consequently not possible to combat each of these various causes individually with a specific, targeted treatment, the only possible therapeutic strategy is to eliminate the troublesome symptoms of these conditions as effectively as

possible, primarily by countering the inflammation or the congestion of the throat, mouth and gums, while simultaneously also alleviating or eliminating the troublesome pain.

[0003] The products usable to treat this complex clinical picture which are currently commercially available may in general terms be divided into two categories. The first of these categories consists of a range of products based on natural substances or extracts, such as propolis, mixtures of honey and wild rose, eugenol and others. The second category, on the other hand, comprises medicinal preparations containing one or more pharmaceutical active ingredients which must combine efficacy with an optimum safety and tolerability profile. These medicinal preparations are generally classified by the European health authorities as "self-medication products", which the patient may accordingly request on his/her own initiative or after consulting a doctor, pharmacist or any other health professional, or in response to advertising messages.

[0004] These pharmaceutical products, although subject to prior approval as medicines by the health regulatory authorities (since they contain one or more active ingredients) and thus frequently sold only in pharmacies (the specific legislation may vary from country to country), may be freely sold directly to any patient requesting them without there being any need to submit a doctor's prescription. This explains the alternative names for these medicines, which are also known as "freely sold products" or "over-the-counter products".

[0005] Taking due account of the above, a medicinal product for self medication to be used as an anti-inflammatory and analgesic for spraying into/onto the mouth, throat and gums must necessarily meet various ideal requirements, including: (a) having satisfactory anti-inflammatory and analgesic activity, both for reducing congestion and for alleviating the associated pain - the active ingredient must furthermore be homogeneously dissolved in the solution so that it can be sprayed uniformly into the oral cavity; (b) the solution must be pharmaceutically stable and the active and auxiliary ingredients must accordingly not react with one another; (c) the solution must be biologically acceptable to the oral mucosa, and thus neither excessively acidic, so as not to attack the dentine, nor excessively basic, so as not to exacerbate the irritation; (d) the provision of a mild disinfectant action to protect the mouth and pharynx from any bacterial and viral attack; (e) the solution must have a preservative action to protect the solution from bacterial contamination and proliferation during production and subsequent use; and (f) the solution must be organoleptically acceptable since it is intended for an organ which is particularly delicate and sensitive to unpleasant flavours and odours.

[0006] An ideal aqueous solution must remain stable for a certain period of time, being clear and transparent without precipitates and contaminants. It will be necessary to avoid certain incompatibilities, such as using parabens with a pH greater than 8.0, introducing a highly reactive inorganic substance, such as for example potassium bicarbonate, into the composition, using edetic acid

and some of the salts thereof which attack the calcium of the dentine ("Handbook of Pharmaceutical Excipients", 4th edition, 2003, American Pharmaceutical Association, page 226, paragraph 14, Safety) or using unstable colorants in order to avoid loss of colour during ageing and so on.

[0007] At present, there is no pharmaceutical composition available which is capable of combining all the ideal features listed above. Indeed, the formulations which may be found in the literature or those already on the market (trade names are deliberately not stated so as not to give rise to any unjustified accusation of unfair competition) lack the majority of the properties listed above.

[0008] The new generation non-steroidal anti-inflammatories, such as for example COX-2 inhibitors (celecoxib, rofecoxib and others), cannot be used topically due their mechanism of action. Other first generation non-steroidal anti-inflammatory drugs (NSAIDs), on the other hand, cannot be used due to the high concentration which is required (ibuprofen, tiaprofenic acid), or due to their known instability in water (acetylsalicylic acid), or also due to their sparing solubility (piroxicam, tenoxicam). Still others are known to have sensitising potential (diflunisal, zomepirac), which makes topical use thereof inadvisable.

[0009] Of the remaining active ingredients, some (naproxen and etodolac) exhibit a predominant anti-inflammatory activity and inadequate analgesic activity, while others conversely exhibit a predominant analgesic activity (ketorolac) and little anti-inflammatory activity. Some products already on the

market occasionally exhibit a pH of greater than 8.0 and are thus not physiologically compatible with the mucosa and furthermore result in harmful dysmicrobism of the oral cavity's saprophytic flora. The physiological pH of the mouth is in fact between 6.7 and 7.5.

[0010] Given that no pharmaceutical composition which is described in the literature or is commercially available is capable of meeting the requirements listed above, there is accordingly an urgent need to fill this gap with a pharmaceutical preparation which combines the features listed above.

SUMMARY OF THE INVENTION

[0011] After various studies and experimental trials, a pharmaceutical preparation combining said features has now surprisingly been found. According to one embodiment of the present invention there is provided a throat, mouth and/or gum sprayable pharmaceutical preparation in the form of an aqueous solution comprising:

(a) a non-steroidal anti-inflammatory drug (NSAID) also having analgesic activity;

(b) a biologically compatible buffer consisting essentially of an organic amine selected from at least one D-glucamine, meglumine, trometamol (tris buffer) and a mixture thereof, in a quantity suitable for buffering the pH of the preparation within the range specified below;

(c) a pH of from 6.5 to 8.0, preferably of between 7.0 and 7.5; and

(d) pharmaceutical grade water;

wherein the NSAID is flurbiprofen.

[0012] According to another embodiment, the present inventions relates to the use of a sprayable pharmaceutical preparation for the manufacture of an anti-inflammatory agent for treating the mouth, throat and/or gums, wherein the pharmaceutical composition is in the form of an aqueous solution comprising:

a nonsteroidal anti-inflammatory drug (NSAID) also having analgesic activity;

a biologically compatible buffering organic amine provided with a free or monosubstituted amino group or a mixture thereof, in a quantity suitable for buffering the pH of the preparation within the range specified below;

a pH within a range of from 6.5 to 8.0; and

pharmaceutical grade water;

wherein the NSAID is flurbiprofen; and

the biologically compatible buffering organic amine is D-glucamine, meglumine, trometamol (tris buffer) or a mixture thereof.

The solution buffered in this manner may furthermore contain:

(a) a mild disinfectant;

(b) one or more preservatives;

(c) other auxiliary ingredients.

[0013] The invention may also relate to the pharmaceutical dosage form based on the solution defined above. Said solution may furthermore be distributed in a container with volume ranging from 10 to 100 ml.

[0014] The invention may also relate to the complete packaged form of the solution defined above, which comprises a container that encloses the buffered solution, provided with a dosing pump and a suitable distributor for spraying the solution directly into the oral cavity.

[0015] The invention may also relate to a process for the production of a solution, as defined above, the apportioning thereof into the final packaging ready for distribution, sale, and use by the patient - said process comprising the following operations:

(1) dissolution of one or more preservatives in more than 50% of the total necessary quantity of water, which has previously been heated to approx. 80°C, and subsequent cooling of the solution to ambient temperature of approx. 25°C;

(2) dissolution of the NSAID in water or better in a mixture of equal proportions of water/ethyl alcohol, with immediate buffering with the selected organic amine to the specified pH;

(3) addition of the other ingredients to the mixture (1);

(4) pouring the solution (2) gradually into the solution (3) and mixing sufficiently;

(5) making up to volume (or weight) with water and, if necessary, adjusting the pH to the specified value with the organic amine; and

(6) apportioning the buffered solution into the container, which is sealed with the dosing pump; a suitable distributor fitted onto the pump and

the system subsequently packaged into a box with a patient information leaflet.

DETAILED DESCRIPTION OF THE EXEMPLARY EMBODIMENT(S)

[0016] The invention will now be illustrated in greater detail in the following description. Preferably the invention provides a pharmaceutical preparation consisting of an aqueous solution which comprises:

(A) a non-steroidal anti-inflammatory drug (NSAID) flurbiprofen in a sufficient quantity in the unit dose to effect a balanced anti-inflammatory and analgesic action.

[0017] Flurbiprofen exhibits an high therapeutic index. Flurbiprofen may be employed as a racemate (or racemic mixture) or as one of its enantiomers, namely (R) – (-) flurbiprofen or (S) – (+) flurbiprofen, and more particularly (R) – (-) flurbiprofen. The selected NSAID is used alone in the solution in a range of concentration within which the optimum concentration has been determined for the type of indication, as shown in Table 1 below:

Table 1

NSAID	Minimum concentration in mg/ml (% wt./vol.)	Maximum concentration in mg/ml (% wt./vol.)	Optimum concentration in mg/ml (% wt./vol.)
Flurbiprofen	**1.5 (0.15%)**	**8.0 (0.8%)**	**2.5 (0.25%)**

[0018] The aqueous solution preferably also comprises:

(B) a biologically compatible organic amine with pronounced buffering properties, present alone or as a mixture, with the buffering amino group in free or partially substituted form, used in a sufficient quantity to maintain the pH of the solution within a specified range close to the physiological pH of the oral cavity.

[0019] The most surprising results have been obtained when the selected buffering organic amine consists of D-glucamine, meglumine, or trometamol (tris buffer). Meglumine in particular, having a methyl monosubstituted amino group and thus a weaker buffering action, as has also been described in the literature (Merck Index 13th ed. / meglumine 1.0% = pH 10.5 and trometamol 0.1% = pH 10.1), is more readily suitable to obtain the desired pH. Trometamol, on the other hand, is also highly advisable, being described in the classic, most reliable textbooks of chemical pharmacology as the only "non-toxic amine" to act as a "biological buffer".

[0020] The desired buffering action is generally obtained at a concentration which varies for each buffering organic amine and is stated in Table 2 below.

Table 2

Buffering substance	Minimum concentration in mg/ml (% wt./vol.)	Maximum concentration in mg/ml (% wt./vol.)
Glucamine	0.35 (0.035%)	1.12 (0.112%)
Meglumine	0.40 (0.04%)	2.4 (0.24%)
Trometamol (tris buffer)	0.10 (0.01%)	0.75 (0.075%)

[0021] The aqueous solution preferably also comprises:

(C) the pH of the solution is within a range between 6.5 and 8.0, preferably between 7.0 and 7.5.

[0022] This pH value is accordingly obtained by buffering the specified quantity of the selected NSAID with the (mono- or disubstituted) buffering organic amine in the quantity required to obtain a biocompatible pH as close as possible to the physiological pH of the mouth, which lies between 6.7 and 7.5. This pH range is furthermore particularly suitable for avoiding any modification of the physiological balance of the saprophytic bacterial flora of the oral cavity.

[0023] The aqueous solution preferably also comprises:

(D) pharmaceutical grade water, such as purified or twice-distilled water, of the quality specified in the usual pharmacopoeias.

[0024] Preferably the pharmaceutical preparation of the invention provides a buffered solution which exhibits further improvements in terms of its pharmaceutical, technical and organoleptic properties.

[0025] The present invention preferably provides a buffered solution which is also suitable for combating superficial infective conditions arising from bacterial or viral infections. As such, there is also an objective requirement to provide:

(E) a mild surface disinfectant which is biologically and pharmaceutically compatible with topical use and is selected

from among those conventionally used for similar topical indications and applications in a quantity which is familiar to the person skilled in the art.

[0026] This substance must furthermore be chemically compatible with the other ingredients of the solution and with the dispensing system used. The disinfectant which is typically selected consists of cetylpyridinium chloride or of glycyrrhizic acid or the ammonium or dipotassium salts thereof, the antibacterial and antiviral properties of which have already been thoroughly described in the literature. The disinfectant substance is present alone in the solution, in a sufficient quantity to exert a specific antibacterial and antiviral action. Besides, glycyrrhizic acid, or the ammonium or dipotassium salt thereof, also exhibits a considerable sweet flavour approx. 50 times more powerful than sucrose.

[0027] The mild disinfectant selected is used alone in the buffered solution in a variable quantity in a range within which the optimum concentration has also been determined, as shown in Table 3 below:

Table 3

Mild disinfectant	Minimum concentration in mg/ml (% wt./vol.)	Maximum concentration in mg/ml (% wt./vol.)	Optimum concentration in mg/ml (% wt./vol.)
Cetylpyridinium chloride	1.0 (0.01%)	6.0 (0.6%)	5.0 (0.5%)
Glycyrrhizic acid or salts thereof	0.8 (0.08%)	1.2 (0.12%)	1.0 (0.1%)

[0028] The buffered solution of the invention may furthermore generally be packaged for preservation, distribution and subsequent use in a multidose container, equipped with a suitable pressure dosing pump which makes it possible to spray the solution uniformly into/onto the throat, mouth and gums. In this case, however, there is a real risk that, due to the reduction in internal pressure arising from repeated use of the pump, contaminated air will enter the container from outside causing accidental contamination or the proliferation of bacterial colonies in the solution itself.

[0029] Thus, unless a more advanced pump is used, which is already commercially available, although at higher cost, and is equipped with a suitable filtration system which sterilizes the air entering the container to compensate the reduction in internal pressure, the buffered solution should preferably also comprise:

> (F) a preservative substance, or a mixture thereof, which is selected from among those conventionally used and in the quantity familiar to the person skilled in the art, in order to achieve sufficient microbiological control of the solution, and is moreover compatible with the topical mode of administration and also from the chemical standpoint not only with the other ingredients of the solution, but also with the components of the multidose system used.

[0030] The typical preservatives selected comprise not only conventional parabens, such as methyl p-hydroxybenzoate or propyl p-hydroxybenzoate,

each of which alone or in combination, but in particular also disodium calcium edetate (i.e. not the simple disodium salt which is capable of attacking the calcium in tooth enamel), or finally sodium benzoate.

[0031] The selected preservative is used in the buffered solution at the appropriate concentration to prevent bacterial contamination and proliferation, as shown in Table 4 below:

Table 4

Preservative substance	Minimum concentration in mg/ml (% wt./vol.)	Maximum concentration in mg/ml (% wt./vol.)
Methyl p-hydroxybenzoate	0.25 (0.025%)	1.15 (0.115%)
Propyl p-hydroxybenzoate	0.03 (0.003%)	0.15 (0.015%)
Disodium calcium edetate	0.1 (0.01%)	1.0 (0.1%)
Sodium benzoate	0.2 (0.02%)	5.0 (0.5%)

[0032] Finally, in order to improve the final technical, pharmaceutical and organoleptic properties of the buffered solution, bearing in mind that flavour is a non-negligible factor in a product which is intended to be sprayed into the oral cavity, preferably the pharmaceutical preparation of the invention is improved from the technical and organoleptic standpoint by the addition of other auxiliary ingredients, as indicated below:

(G) The nature, the quality and the concentration of each individual auxiliary ingredient varies from case to case

depending on the starting buffered solution and on the final properties of the preparation which it is desired to obtain.

[0033] With regard to the quality of an individual auxiliary ingredient, a person skilled in the art will certainly be capable of selecting that which complies with the quality specifications stated in the specific monograph published in one of the main pharmacopoeias (Eur. Ph., USP, JP, FU, BP). In the absence of a specific monograph, the person skilled in the art will be able to select the auxiliary ingredient with properties which comply as well as possible with those stated in specialist publications, such as for example "Remington: The Science and Practice of Pharmacy", 20th Edition, editors A.R. Gennaro et al., University of the Sciences in Philadelphia College or "Handbook of Pharmaceutical Excipients", 4th Edition, 2003, American Pharmaceutical Association.

[0034] The following Examples provide purely indicative examples of specific auxiliary ingredients and the associated optimum concentrations for each buffered solution illustrated in the Examples themselves. The preferred auxiliary ingredients which are selected and thus also the concentration thereof are accordingly not binding for each buffered solution and do not limit the invention, it being possible to replace each of them suitably with another similar ingredient while still obtaining a result which is comparable overall with that of the invention itself.

[0035] Nevertheless, with regard to the quality and quantity thereof stated in the Examples, these ingredients are the result of careful optimisation which

was not carried out casually but also involved an inventive step. The preferred auxiliary ingredients for the following Examples are stated below:

- glycerol (viscosity agent)
- sorbitol, xylitol (sweetening agent)
- ethyl alcohol (fluidising agent)
- castor oil 40 polyethoxylate (thickening agent)
- saccharin sodium, acesulfame potassium (sweeteners)
- mint essence, natural mint flavour, natural peach flavour (natural essences or flavours)
- patent blue V-E131, E-124 (colours).

[0036] Preferably the invention provides a pharmaceutical preparation wherein xylitol is used as a non-cariogenic sweetening agent. It will be appreciated that xylitol is not utilized by microorganisms and does not promote dental plaque with the associated cariogenic effects. However, xylitol exerts certain bacteriostatic and bactericidal affects, particularly against common spoilage organisms, thus enhancing the stability and freshness of the composition. Moreover, it will be appreciated that a solution according to a preferred embodiment of the invention containing xylitol is also not contraindicated in diabetic or carbohydrate-controlled diets.

[0037] A solution according to one embodiment of the invention is prepared in the above-stated sequence using the methods and machinery conventionally used in the pharmaceutical sector, but this is neither mandatory nor does it limit the invention itself. Indeed, adjustments remain

possible with regard to the specific formulation used, the overall volume of the batch to be prepared, while nevertheless obtaining a result which is comparable overall with that of the invention itself.

[0038] The solution may generally be packaged for preservation, distribution, sale and use in a suitable container provided with a dosing pump with an associated distributor, in such a manner that it may readily be sprayed directly into/onto the mouth, throat and gums. In particular, the solution is preferably packaged in a multidose container equipped with a pressure operating pump, fitted with a dispensing erogator (of variable type and shape) which enables uniform spraying of the solution within the oral cavity.

[0039] In general, the volume of solution sprayed for each dose varies as a function of the concentration of the active ingredient, but for the formulations of the Examples, the ideal volume to be sprayed for each dose ranges from 100 to 300 microlitres, with an amount of 200 microlitres preferably being sprayed for each unit dose.

[0040] The pharmaceutical preparation of the invention may be useful for the topical treatment of inflammatory conditions of the mouth, throat and gums with accompanying pain and, where the composition also contains a mild disinfectant, also for combatting the condition brought about by the bacterial and viral component which is often associated therewith. The preparation may also be useful in reducing the inflammation/congestion and associated pain of the mucosa of the oral cavity.

[0041] Examples of typical buffered solutions of the invention are presented below in tabular form in order to make the individual details more readily discernible. These Examples are provided with the aim of better illustrating the invention and thus do not constitute any limitation of the invention itself, it being obvious that the spirit and scope of the invention also include any other modifications which are obvious to the person skilled in the art.

EXAMPLES 1 TO 3

INGREDIENT	TYPE		EXAMPLES 1 TO 3 (mg/ml)		
			1	2	3
Flurbiprofen	A	mg	2.50	2.50	2.50
Glucamine to make up to pH(C)	B	mg	---	---	---
Meglumine to make up to pH(C)	B	mg	÷ 2.10	÷ 2.15	÷ 0.70
Trometamol to make up to pH(C)	B	mg	---	---	÷ 0.40
pH	C		7.10	7.30	7.20
Cetylpyridinium chloride	E	mg	---	---	---
Glycyrrhizic acid	E	mg	---	---	---
Methyl p-hydroxybenzoate	F	mg	1.00	---	1.00
Propyl p-hydroxybenzoate	F	mg	0.20	---	0.20
Disodium calcium edetate	F	mg	---	0.50	---
Sodium benzoate	F	mg	---	---	---
Glycerol	G	mg	100.00	100.00	100.00
Sorbitol	G	mg	70.00	70.00	70.00
Xylitol	G	mg	---	---	---
Ethyl alcohol (96%)	G	mg	100.00	100.00	100.00
Hydrogenated castor oil 40 polyethoxylate	G	mg	24.00	24.00	24.00
Saccharin sodium	G	mg	1.50	1.50	1.50
Acesulfame potassium	G	mg	---	---	---
Mint essence	G	mg	6.00	6.00	6.00
Natural mint flavour	G	mg	---	---	---
Natural peach flavour	G	mg	---	---	---
Patent blue V-E131	G	mg	---	0.006	---
Colour E124	G	mg	---	---	---
Purified water up to volume	D	ml	1.00	1.00	1.00

(A) =Active ingredient
(B) =Buffering organic amine
(C) =pH
(D) =Water (pharmaceutical grade)
(E) =Disinfectant
(F) =Preservative
(G) = Auxiliary ingredient

[0042] The following compositions are prepared as described in the method of the subsequent Example.

EXAMPLES 4 & 5

INGREDIENT	TYPE		EXAMPLES 4 & 5 (mg/ml)	
			4	5
Flurbiprofen	A	mg	2.50	2.50
Glucamine to make up to pH (C)	B	mg	---	÷ 1.00
Meglumine to make up to pH (C)	B	mg	÷ 2.30	---
Trometamol to make up to pH (C)	B	mg	---	---
pH	C		7.00	7.50
Cetylpyridinium chloride	E	mg	5.00	---
Glycyrrhizic acid	E	mg	---	1.00
Methyl p-hydroxybenzoate	F	mg	1.00	---
Propyl p-hydroxybenzoate	F	mg	0.20	---
Disodium calcium edetate	F	mg	---	0.50
Sodium benzoate	F	mg	---	---
Glycerol	G	mg	100.00	100.00
Sorbitol	G	mg	70.00	70.00
Xylitol	G	mg	---	---
Ethyl alcohol (96%)	G	mg	100.00	100.00
Hydrogenated castor oil 40 polyethoxylate	G	mg	24.00	24.00
Saccharin sodium	G	mg	1.50	1.50
Acesulfame potassium	G	mg	---	---
Mint essence	G	mg	6.00	6.00
Natural mint flavour	G	mg	---	---
Natural peach flavour	G	mg	---	---
Patent blue V-E131	G	mg	---	0.006
Colour E124	G	mg	---	---
Purified water up to volume	D	ml	1.00	1.00

(A) =Active ingredient
(B) =Buffering organic amine
(C) =pH
(D) =Water (pharmaceutical grade)
(E) =Disinfectant
(F) =Preservative
(G) =Auxiliary ingredient

[0043] The following compositions are prepared as described in the method of the subsequent Example.

EXAMPLES 6 & 7

INGREDIENT	TYPE		EXAMPLES 6 & 7 (mg/ml)	
			6	7
Flurbiprofen	A	mg	2.50	2.50
Glucamine to make up to pH (C)	B	mg	---	---
Meglumine to make up to pH (C)	B	mg	÷ 2.10	---
Trometamol to make up to pH (C)	B	mg	---	÷ 0.70
pH	C		7.10	7.40
Cetylpyridinium chloride	E	mg	---	---
Glycyrrhizic acid	E	mg	---	---
Methyl p-hydroxybenzoate	F	mg	1.00	1.00
Propyl p-hydroxybenzoate	F	mg	0.20	0.20
Disodium calcium edetate	F	mg	---	---
Sodium benzoate	F	mg	---	---
Glycerol	G	mg	100.00	100.00
Sorbitol	G	mg	---	---
Xylitol	G	mg	70.00	70.00
Ethyl alcohol (96%)	G	mg	100.00	100.00
Hydrogenated castor oil 40 polyethoxylate	G	mg	24.00	24.00
Saccharin sodium	G	mg	1.50	1.50
Acesulfame potassium	G	mg	---	---
Mint essence	G	mg	6.00	6.00
Natural mint flavour	G	mg	---	---
Natural peach flavour	G	mg	---	---
Patent blue V-E131	G	mg	---	0.006
Colour E124	G	mg	---	---
Purified water up to volume	D	ml	1.00	1.00

(A) =Active ingredient
(B) =Buffering organic amine
(C) =pH
(D) =Water (pharmaceutical grade)
(E) =Disinfectant
(F) =Preservative
(G) =Auxiliary ingredient

[0044] The following compositions are prepared as described in the method of the subsequent Example.

EXAMPLE 8

Preparation of 2000 vials containing 15 ml of solution for spraying according to the composition of Example 1. Production for 2000 vials containing 15 ml of solution for spraying:

Ingredient	**15 ml vial**		**Total**	
Flurbiprofen	**37.50**	**mg**	**75.00**	**g**
Meglumine to make up to pH (C)	**÷ 31.50**	**mg**	**÷ 63.00**	**g**
pH	**7.10**		**7.10**	
Methyl p-hydroxybenzoate	**15.00**	**mg**	**30.00**	**g**
Propyl p-hydroxybenzoate	**3.00**	**mg**	**6.00**	**g**
Glycerol	**1.50**	**g**	**3.00**	**kg**
Sorbitol	**1.05**	**g**	**2.10**	**kg**
Ethyl alcohol (96%)	**1.50**	**g**	**3.10**	**kg**
Hydrogenated castor oil 40 polyethoxylate	**360.00**	**mg**	**720.00**	**g**
Saccharin sodium	**22.50**	**mg**	**45.00**	**g**
Mint essence	**90.00**	**mg**	**180.00**	**g**
Purified water up to volume	**15.00**	**ml**	**30.00**	**l**

Phase 1 **-** Solution A

20 litres of purified water are placed in a suitable stainless steel dissolver and adjusted to approx. 80°C. Completely dissolve 30.0 g of methyl p-hydroxybenzoate and 6.0 g of propyl p-hydroxybenzoate. Cool the solution to ambient temperature (25°C).

Phase 2 **-** Solution B

3 litres of water and 3.0 kg of 96% ethyl alcohol are mixed in a suitable stainless steel container at approx. 30°C. Then add 75.0 g of flurbiprofen and buffer to pH 7.1 with meglumine (approx. 63 g).

Phase 3 **-** Solution C

While continuously stirring solution A, add the other ingredients: 3.0 kg of glycerol, 2.1 kg of sorbitol, 720.0 g of hydrogenated castor oil 40 polyethoxylate, 45.0 g of saccharin sodium and 180.0 g of mint essence. Stir until dissolution is complete.

Phase 4 **-** Buffered solution

Adjust the volume to 30 litres by adding purified water and check the pH. If necessary, buffer the pH to the desired value of 7.1 by adding meglumine.

[0045] The buffered solution is then apportioned into the vials which are sealed with the dosing pump equipped with a dispensing erogator. The system is then packaged in a suitable box. In this manner, 1865 vials each of 15 ml are obtained.

[0046] While certain embodiments of the present invention are described in detail above, the scope of the invention is not to be considered limited by such disclosure, and modifications are possible without departing from the spirit of the invention as evidenced by the following claims: